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2,804,460

TROPENE DERIVATIVES

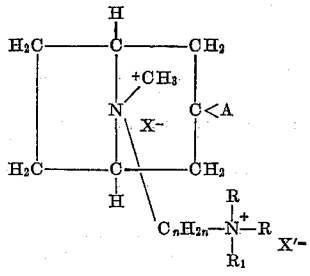
Chester J. Cavallito, Allan Poe Gray, and Wesley Lea Archer, Decatur, Ill., assignors to Irwin, Neisler and Company, Decatur, Ill., a corporation of Illinois

No Drawing. Application July 15, 1955, Serial No. 522,393

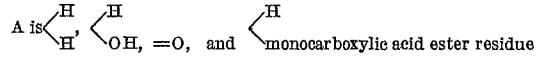
6 Claims. (Cl. 260—292)

This invention relates to novel organic compounds and is more particularly concerned with certain diquaternary ammonio derivatives of tropane, tropine, and tropine-like materials.

Specifically, the compounds of the present invention have the following formula:



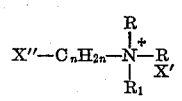
wherein n is an integer from two to four, inclusive, R and R_1 are lower-alkyl, and wherein said R and R_1 may be the same, different or joined together to form an N-heterocyclic group, the sum of the carbon atoms in said R's and R_1 being from three to six, inclusive,



and X and X′ are stable, non-toxic anions.

The compounds of the present invention are crystalline solids having relatively high melting points and are water soluble. Preliminary pharmacological testing of these compounds has indicated that they have utility as hypotensive agents. A distinct advantage accruing from the use of the present compounds in animals has indicated that a floor-level blood pressure fall is obtained, after certain minimum dosage has been administered. It can be administered at a very high relative dosage without causing untoward effects in both mice and monkeys when compared to presently employed hypotensive agents. Further, after an initial dosage of the compounds of the present invention in animals, the maintenance dosage required to keep the blood pressure at a reduced level is substantially less than would normally be expected. Intravenous administration in an aqueous solution has been the usual method of administration.

Preparation of the compounds of the present invention may be readily accomplished by providing an appropriate tropane, tropine or tropine-like derivative, and reacting this material with a suitable halodimethylene, trimethylene or tetramethylene quaternary ammonium salt having the following formula:



wherein n, R's, R_1 and X′ have the hereinbefore assigned values and X″ is a halogen selected from the group consisting of chlorine, bromine and iodine. Reaction is normally accomplished by mixing the two reactants in a suitable solvent, such as acetonitrile, alcohols such as ethanol, methanol, isopropyl alcohol, propyl alcohol, isoamyl alcohol, et cetera; nitrobenzene, nitromethane, nitroethane, mixtures of dioxane and an alcohol and other polar solvents and solvent mixtures, et cetera. Normally, to insure an efficient reaction, a somewhat elevated temperature is employed, however, room temperature to 150 degrees centigrade is satisfactory and a reflux temperature of about eighty to ninety degrees centigrade is preferred. Upon completion of the reaction, the reaction product may be recovered by cooling the reaction mixture and separating the crystals which form. Purification of these crystals is accomplished in conventional manner, as by recrystallization from an appropriate solvent.

The starting materials employed in the process of the present invention are well known in the art, and others are described in a copending application of C. J. Cavallito and A. P. Gray, Serial 406,052, filed January 25, 1954. One starting material which is readily available and applicable for preparing compounds of the present invention is atropine, which is a tropane derivative containing a substituent hydrogen and an alpha-(hydroxymethyl)-phenylacetic acid residue (tropic acid residue) attached to the same carbon atom. Other monocarboxylic acid ester residues which are suitable include alkanoic, aromatic and aralkanoic containing up to 15 carbon atoms, such as, for example, acetoxy, propionoxy, butyroxy, benzoxy, 5-(beta-naphthyl)-valeroxy, 3-dimethylbutyroxy, alpha-naphthalene carboxy, veratroxy, diphenylacetoxy, 9-fluorenecarboxy, phenylacetoxy, etc. The term "stable, non-toxic anions" as used herein, is intended to include those which form stable quaternary salts with the type of materials here employed and which are substantially non-toxic when administered as hypotensive agents. Representative anions which are suitable, include, for example, the chloride, bromide, iodide, sulfate, nitrate, citrate, lactate, tartrate, tannate, malate, et cetera.

The following examples are given to illustrate the procedure of the present invention, but are not to be construed as limiting.

Example 1

A solution of 33.6 grams (0.25 mole) of tropine and 68.0 grams (0.25 mole) of 3-bromopropyltrimethylammonium bromide in 300 milliliters of acetonitrile was refluxed for 24 hours. An oily precipitate formed which was collected and recrystallized from ethyl alcohol and ethyl acetate. There was thus obtained 63.0 grams (63 percent of the theoretical yield) of 1-tropinium-3-(trimethylammonium)-propane dibromide, melting with gas evolution at 247 degrees centigrade.

Analysis.—Calculated: C, 41.80; H, 7.52; Br, 39.74. Found: C, 42.03; H, 7.71; Br, 39.47.

Example 2

A solution of 7.7 grams (0.055 mole) of tropine and 16.4 grams (0.055 mole) of 3-bromopropylmethylpiperidinium bromide in 100 milliliters of acetonitrile was refluxed on a steam bath for three hours. At the end of this period, the crystalline product was filtered from the warm solution and recrystallized twice from a mixture of ethanol and ethyl acetate to yield 5.15 grams of 1-tropinium-3-(N-methylpiperidinium)-propane dibromide, as fine white needles, which darken above 230 degrees centigrade and melt above 270 degrees centigrade.

Analysis.—Calculated: C, 46.16; H, 7.75; Br, 36.14. Found: C, 46.50; H, 7.53; Br, 36.02.

Example 3

A solution containing 10.0 grams (0.071 mole) of tropine and 20.4 grams (0.071 mole) of 3-bromopropylmethylpyrrolidinium bromide in 100 milliliters of acetonitrile was refluxed on the steam bath for five hours. At the end of this time, the crude crystalline product was filtered from the warm solution and recrystallized twice from ethanol and ethyl acetate to yield 17.2 grams (57 percent of the theoretical yield) of 1-tropinium-3-(N-methylpyrrolidinium)-propane dibromide, as white crystals which darken at 235 degrees centigrade and decompose at about 268 degrees centigrade.

Analysis.—Calculated: C, 44.87; H, 7.53; Br, 37.32. Found: C, 44.93; H, 7.23; Br, 36.93. In a manner similar to that of the above examples, 1-tropanium-3-(trimethylammonium)-propane dibromide, melting above 270 degrees centigrade is obtained.

Analysis.—Calculated: C, 43.53; H, 7.83; Br, 41.38. Found: C, 43.38; H, 7.95; Br, 41.02.

Atropine may be reacted with 3-bromopropyltrimethylammonium bromide to yield 1-atropinium-3-(trimethylammonium)-propane dibromide melting at 207 degrees centigrade.

Analysis.—Calculated: C, 50.18; H, 6.96; Br, 29.04. Found: C, 50.36; H, 7.03; Br, 29.22.

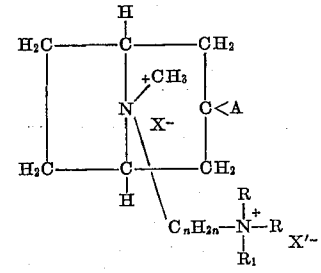
Tropinone may be reacted with 3-bromopropyltrimethylammonium bromide to yield 1-tropinonium-3-(trimethylammonium)-propane dibromide having a melting point of 204 degrees centigrade.

Analysis.—Calculated: C, 42.01; H, 7.05; Br, 39.94. Found: C, 42.61; H, 7.35; Br, 39.62.

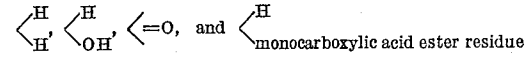
Various modifications may be made in the present invention without departing from the spirit or scope thereof and it is to be understood that we limit ourselves only as defined in the appended claims.

We claim:

1. A compound having the formula:



wherein *n* is an integer from two to four, inclusive, R and R_1 represent lower-alkyl radicals which may be joined together to form an N-heterocyclic group, the sum of the carbon atoms in said radicals and group being from three to six, inclusive, <A is selected from the group consisting of



and wherein X and X′ are stable, non-toxic anions.

2. 1-tropinium-3-(trimethylammonium)-propane dibromide.

3. 1-tropinium-3-(N-methylpyrrolidinium)-propane dibromide.

4. 1-tropanium-3-(trimethylammonium)-propane dibromide.

5. 1-atropinium-3-(trimethylammonium)-propane dibromide.

6. 1-tropinonium-3-(trimethylammonium)-propane dibromide.

No references cited.